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Application of dietary supplements in the prevention of type 2 diabetes-related cardiovascular complications

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Yannan Jin¹, Randolph RJ Arroo^{2*}

¹ School of Allied Health Sciences, Faculty of Health & Life Sciences, De Montfort University, The Gateway, Leicester LE1 9BH, United Kingdom

² Leicester School of Pharmacy, Faculty of Health & Life Sciences, De Montfort University, The Gateway, Leicester LE1 9BH, United Kingdom

* Corresponding Author, Email: rrjarroo@dmu.ac.uk

Abstract

Type 2 diabetes, which accounts for the vast majority of diabetes worldwide is the result of a lowered sensitivity of the insulin receptors, resulting in impaired sugar metabolism and chronic hyperglycaemia. There is no cure for type 2 diabetes, though some people with pre-diabetes and diabetes manage to reach and hold normal blood sugar levels, thus avoiding most of the complications that come with chronic hyperglycaemia; this is sometimes referred to as 'reversing diabetes'. A healthy diet, with sufficient amounts of fruits, nuts, and vegetables is positively correlated with maintaining glycaemic control and prevention of diabetes-related complications.

Whereas many different dietary phytochemicals have been considered to play a role in the glycaemic control and in prevention of degenerative diseases, there is currently no consensus on a particular mode of action. In this review, a range of pre-clinical studies and intervention studies, including randomised double-blind, placebo controlled clinical studies, are considered that investigate the role of dietary compounds in the prevention of type 2 diabetes-related complications. Three generic mechanisms of action can be discerned: compounds that reduce sugar uptake, compounds that restore insulin function, and compounds that attenuate the effects of oxidative stress and chronic inflammation. Particularly the latter has received wide attention in the form of activation of the Nrf2-antioxidant response element signalling pathway by various polyphenolic or triterpenoid compounds. Although individual reports may present models with clear looking signalling cascades, an overall review shows that many biologically active compounds in the human diet are pan assay interference substances that alter several cell functions simultaneously, which makes them less attractive for drug development.

Key words: Flavonoids; oxidative stress; inflammation; pan assay interference substances; homeostasis

Diabetes

Diabetes is a metabolic disorder characterised by prolonged high blood sugar levels (hyperglycaemia). Assessment of blood sugar levels is typically done by measuring the level of glucose in small blood samples after overnight fasting (fasting blood sugar); levels less than 100mg/dL (5.6mM) are considered healthy, 100-125mg/dL (5.6-6.9mM) is considered pre-diabetes, and more than 126mg/dL (>7mM) is considered diabetes.

In 2019, 351.7 million people of working age (20–64 years) had diagnosed or undiagnosed diabetes. This number is expected to rise to 417.3 million by 2030. The largest increase is expected to take place in the regions where economies are moving from low- to middle-income status (Williams et al., 2019)

Type 2 diabetes (T2D), which accounts for the vast majority (around 90%) of diabetes worldwide (Williams et al., 2019), is the result of a lowered sensitivity of the insulin receptors notably on cells in the liver and muscles. The insulin resistance is often initially compensated by β -cell hypersecretion of insulin (hyperinsulinaemia); prescription drugs like sulfonylureas work by stimulating β -cells to more activity. However, in advanced stages the β -cells, located in the islets of Langerhans of the pancreas, eventually are no longer able to secrete enough insulin (hypoinsulinaemia). Abnormal insulin sensitivity commonly precedes the clinical diagnosis of diabetes by up to 15 years (Zaccardi et al. 2015).

Insulin signalling pathways are triggered by the binding of insulin to the transmembrane insulin receptor. This induces auto-phosphorylation in tyrosine residues of the receptor followed by downstream cascading events which create a suitable binding site for insulin receptor substrate proteins (IRSs), which is then activated via phosphorylation by different insulin-induced kinases such as PKC, SIK2, AKT, S6K1, mTOR, ERK1/2, and ROCK1. Insulin-independent kinases, such as AMPK and GSK3, in turn phosphorylate IRSs and trigger downstream signal transduction. Though the exact pathophysiology of insulin

resistance is unclear, defects in insulin signal transduction play a prominent role (Yaribeygi et al., 2018). The biguanide metformin (**1**) (Fig. 1) is commonly prescribed to delay the loss of insulin sensitivity in the liver, muscle, and adipose tissue, but the exact molecular mechanism of this drug is not yet completely understood. Metformin is an analogue of galegine (**2**), a naturally occurring guanidine found in *Galega officinalis* L. which was also used to treat diabetes but is now considered obsolete (Bailey & Day, 2004).

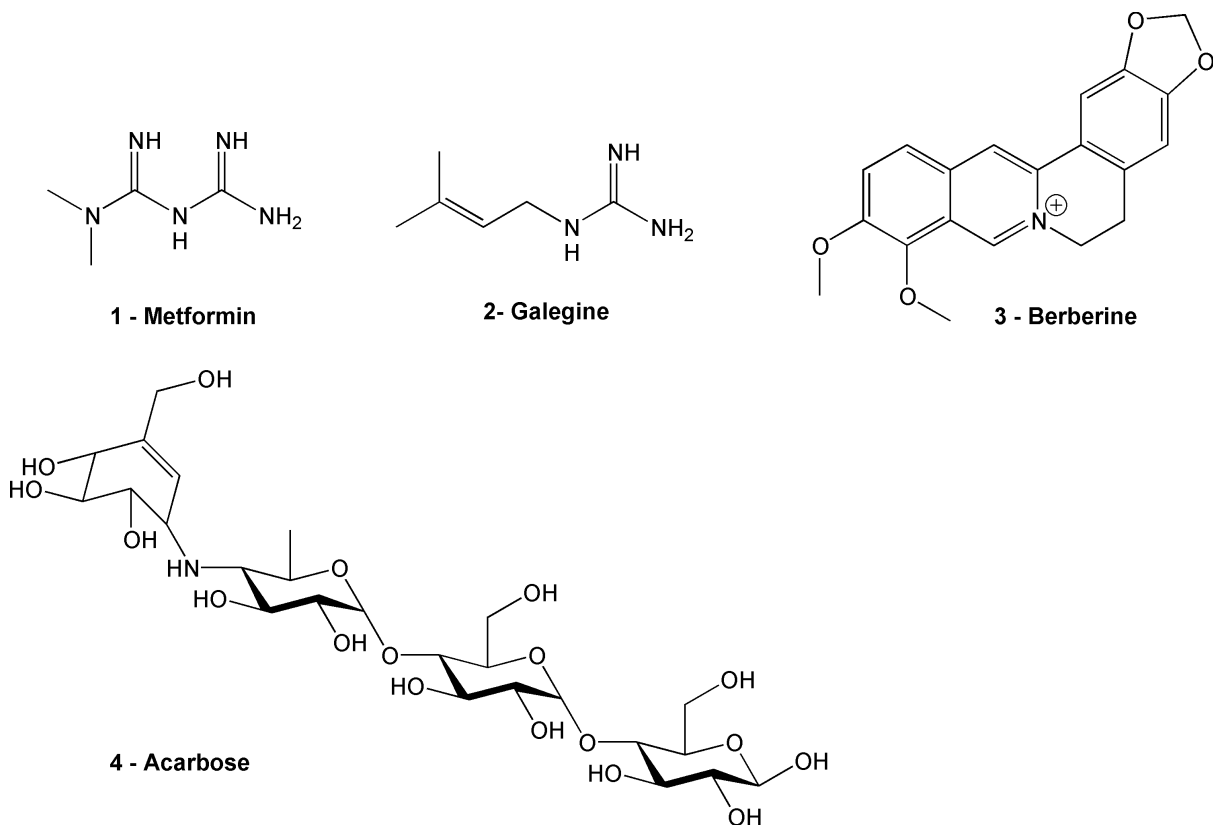


Fig 1: Compounds with known antidiabetic activity

Diabetes is linked with roughly doubling the risk for a wide range of vascular diseases, and data based on a study with 302 430 participants are consistent with a causal association, although the causal component or components in this pathway have not yet been identified (Sarwar et al., 2010, Sarwar & Danesh, 2010). Diabetes is also associated with premature death from infectious diseases, several types of cancer, and degenerative disorders. However, causal links are still unclear. The associations might be due to hyperglycemia or other

biologic factors such as insulin resistance or hyperinsulinemia, or due to shared risk factors (e.g., obesity) or a combination of these (Seshasai et al., 2011).

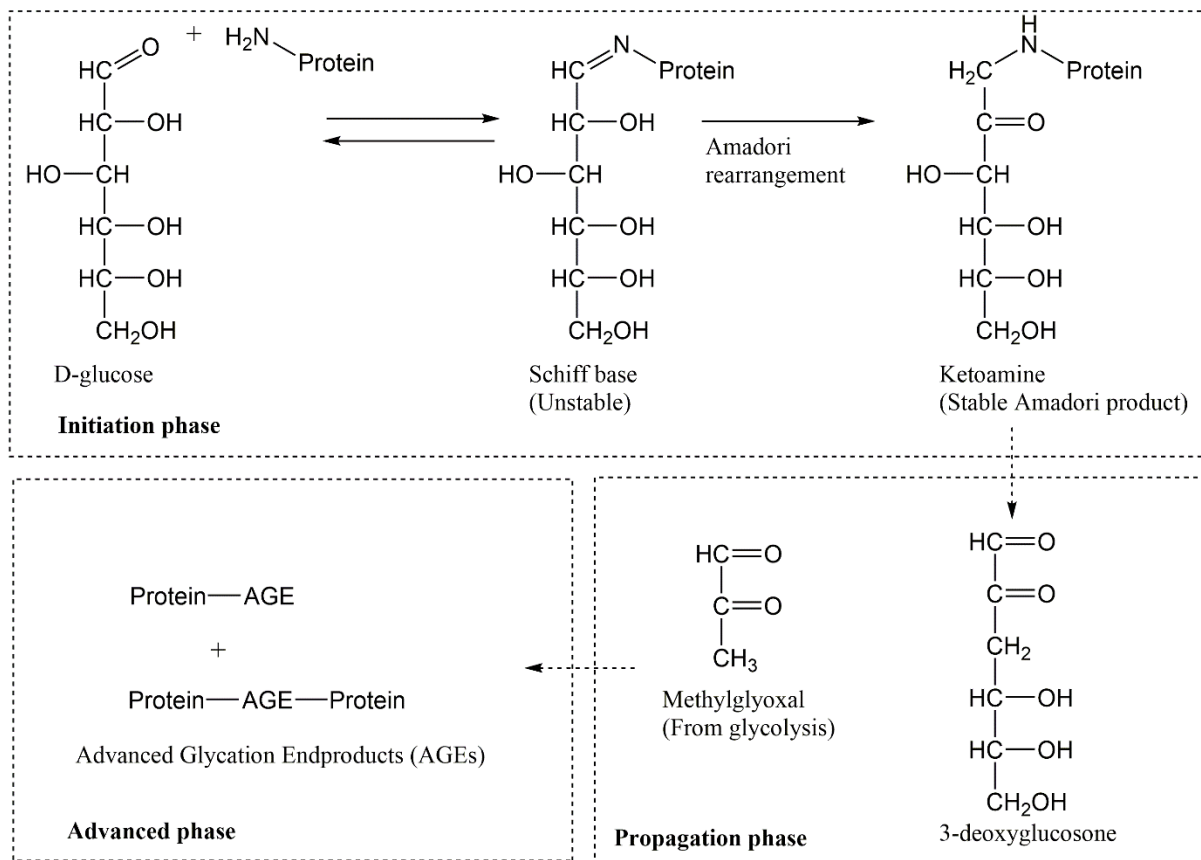


Fig 2: Formation of Advance Glycation Endproducts (AGEs)

Chronic hyperglycaemia can result in a number of complications. High levels of glucose or fructose in the blood plasma can initially result in glycation reaction, i.e. nonenzymatic attachment of a monosaccharide to the N-terminus of a protein or to the amino groups of arginine or lysine residues followed by Amadori rearrangement resulting in the formation of a ketoamine (Fig. 2). Glycation should not be confused with glycosylation, the enzyme-controlled post-transcriptional process that occurs during synthesis of glycoproteins as part of normal healthy physiology. Glycation occurs continuously over the lifetime of the protein, so the concentration of glycated haemoglobin (HbA1c) levels can be used as a measure of the average blood glucose value over a period of time (Welsh et al., 2016). HbA1c levels are a

measure for blood glucose management, and can be tested every three months – a normal HbA1c target is below 48mmol/mol (or 6.5% on the older measurement scale). People who are at risk of hypoglycemia, or for whom tight blood glucose regulation is not advised, may be advised to keep their HbA1c below 59 mmols/mol (under 7.5% in the old percentage units).

After the initiation phase of glycation, a propagation phase starts where Amadori products are degraded resulting in the formation of free radicals and reactive dicarbonyl species, e.g. 3-deoxyglucosone. Additional reactive dicarbonyls, e.g. methylglyoxal which is formed as by product of glycolysis, also add to the propagation of glycation. Finally, in the advanced phase, advanced glycation products (AGEs) are formed, and the interaction between AGEs and their receptor, RAGE, is considered to be a main cause of chronic diseases, oxidative stress, and a state of low-grade chronic inflammation (Brownlee 2001; Peyroux & Sternberg, 2006; Yeh et al., 2017a, 2017b; Fournet et al., 2018). During normal metabolism, methylglyoxal and other reactive aldehydes are detoxified by the glyoxalase system, but chronic hyperglycaemia can eventually overwhelm this detoxification process, resulting in the accumulation of AGEs.

Interaction of AGEs with RAGE on the membrane of cells such as macrophages, mesangial or endothelial cells, pericytes, causes intracellular oxidative stress and activation of nuclear factor NF- κ B via activation of the mitogen-activated protein (MAP) kinase signalling pathway

Role of diet

Occurrence of T2D is correlated with lifestyle and dietary patterns; notably, greater consumption of sugar-rich foods is correlated with increased levels of T2D (Basu et al.,

2013). Although currently there is no cure for T2D, some people with pre-diabetes and diabetes manage to reach and hold normal blood sugar levels, and thus avoid most of the complications that come with prolonged hyperglycaemia; this is sometimes referred to as ‘reversing diabetes’. For overweight or obese individuals with T2D, a weight loss of at least 5% was shown to improve circulating glucose and lipid levels over 12 months (Franz et al., 2015). A 3-year randomized clinical trial followed by 7-years of open-label modified intervention follow-up showed that regular moderate exercise and a healthy diet over a 10-year period reduced the absolute risk of getting diabetes by 25.9% (Herman et al., 2013). Systematic reviews and meta-analyses of dietary patterns have indicated that regular consumption of red meat, processed meat, and sugar-sweetened beverages is linked with an increased incidence of T2D, whereas increased consumption of whole grains, fruits, and dairy is linked with a lowered risk of becoming diabetic (Medina-Remón et al., 2017; Schwingshackl et al., 2017).

Diabetes is a chronic condition, and it takes continuous effort to attain adequate glycemic control amongst diabetic patients. Individuals with T2D are commonly treated with multiple-medication regimens - some to achieve glycemic control, others to treat diabetic complications - to an average of four prescription medications per patient per day. In addition, weight loss is often advised in management of T2D (Gonzalez et al., 2016).

Diabetes places a significant self-management burden on affected individuals and families, but available evidence suggests that diabetes among the illnesses with the lowest levels of adequate self-management, especially for regimen aspects involving lifestyle change. Non-adherence to prescription medicines is common, and patients often look to alternative forms of therapy such as herbal medicines (Ezuruike & Prieto, 2014). Meta analyses of the use of herbal medicines to manage T2D, e.g. berberine (**3**) from *Coptis chinensis* Franch (‘Huanglian’) in Chinese Herbal Medicine, or extracts of bitter melon (*Momordica charantia*

L.) as in Asia, Brazil, and east Africa, have indicated some efficacy, although authors warn for the risk of bias in the included studies (Lan et al., 2015; Peter et al., 2019). More methodologically sound large controlled trials, using standardized preparations, are required to more clearly quantify the therapeutic effect of herbal preparations.

Mechanism studies

There is a general consensus that a diet rich in fruit, vegetables, and high in fibre is beneficial for maintaining blood sugar levels within reasonable limits, and for slowing down or averting diabetes-related complications. However, there is no canonical vision on any particular dietary compounds that can be considered the main active pharmaceutical ingredient. Neither is there a consensus on any one particular mechanism of action. Rather three generic mechanisms of action can be discerned: compounds that reduce sugar uptake, compounds that restore insulin function, and compounds that attenuate the effects of oxidative stress and chronic inflammation.

The prescription drug acarbose (**4**) (Glucobay™, Precose™, Prandase™) prevents hydrolysis of starches into glucose. Similarly, several dietary flavonoids (**5**) (Fig. 3) also effectively inhibit the activity of α -amylase and α -glucosidase (Xiao et al., 2013a,b; Zhu et al., 2020). Acarbose causes adverse effects such as bloating, flatulence, or diarrhoea, and this is often used as a justification to look for natural alternatives. However, arguably any compound that inhibits degradation of complex carbohydrates will result in delivery of these carbohydrates to the colon where they are digested by bacteria, causing gastrointestinal side-effects. Papers on α -amylase and α -glucosidase inhibitors tend to report results of in vitro enzyme inhibition assays - sometimes backed up by in silico docking studies, but often omit data on in vivo efficacy or side effects of flavonoids or herbal preparations. In a similar fashion, phytic acid

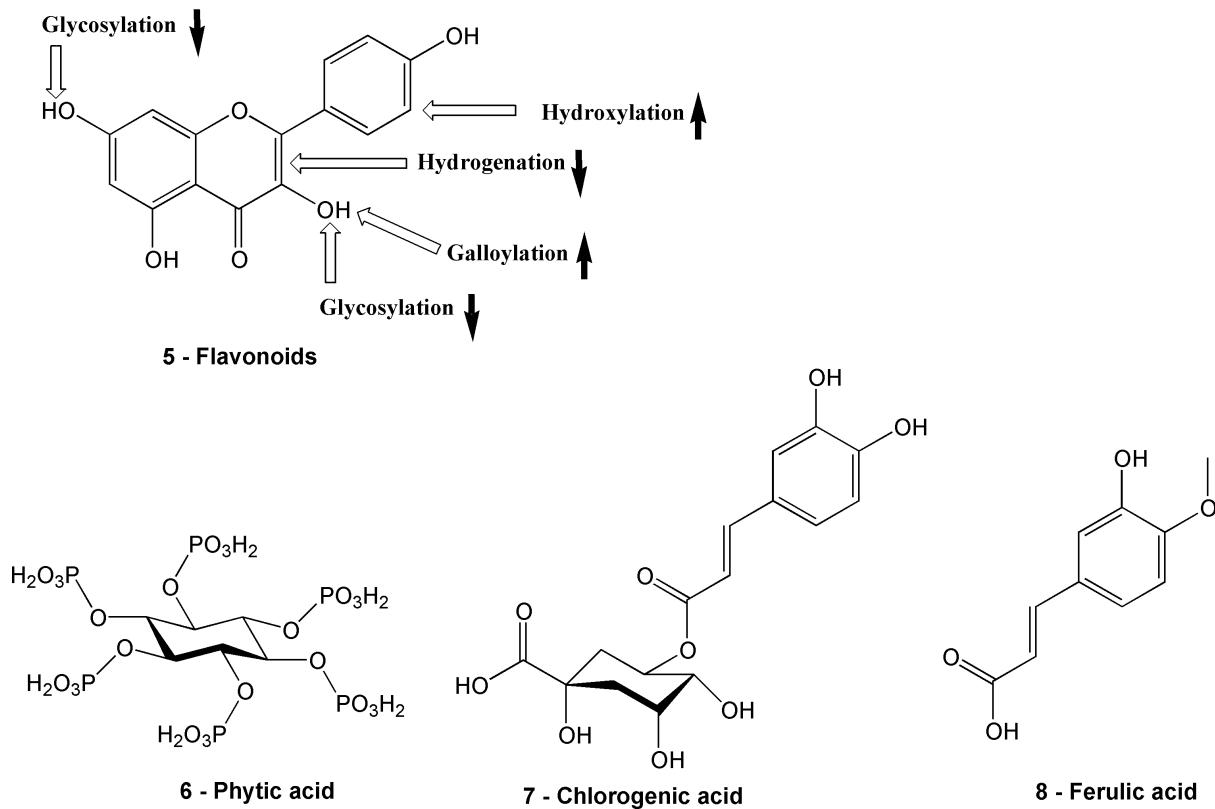


Fig. 3: *Inhibitors of carbohydrate digestion and glucose absorption*

or phytate (**6**), normally present in the aleurone layer of cereals though often lost in the milling process, hinders digestion by binding with starch and starch-associated protein (Biskup et al., 2017). Some simple phenolics, e.g. chlorogenic acid (**7**) and ferulic acid (**8**) have exhibited the ability to block glucose transporter SGLT1, and thus inhibit glucose absorption from the small intestine and glucose reabsorption in the kidneys (Biskup et al., 2017).

The isoflavone genistein (**9**) (Fig. 4) enhanced activity of adenylate cyclase activity in a dose-dependent way (10nM - 5 μ M) in insulin-secreting murine cell lines INS-1 and MIN6 and in vitro cultured mouse pancreatic islets. The resulting rise in intracellular cAMP activated protein kinase A, and overall led to an insulinotropic effect (Liu et al., 2006). Studies on in vitro grown cell cultures (human HepG2 liver carcinoma and 3T3-L1 murine adipocytes) have shown that anthocyanins (**10**) and epicatechins (**11**, **12**), and the alkaloid berberine (**3**)

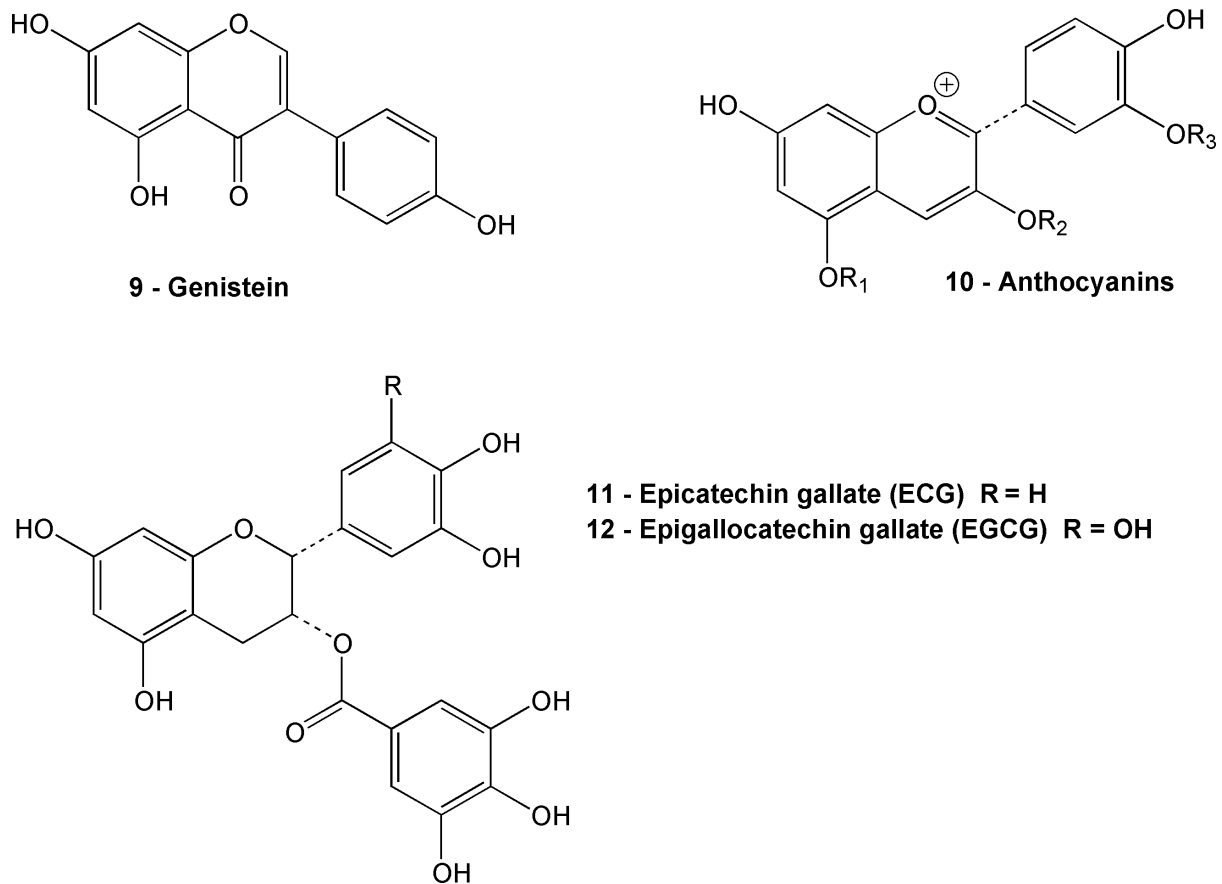


Fig. 4: Compounds that can restore activity of the insulin receptor

can restore activity of the insulin receptor (IR), and trigger phosphorylation of insulin receptor substrate (IRS) resulting in the activation of the PI3K/Akt2 signalling pathway which simultaneously decreases gluconeogenesis and increases glucose uptake by translocating the glucose transporter 4 (GLUT-4) from intracellular stores to the plasma membrane. The results of in vitro studies were confirmed in in vivo studies with streptozotocin (STZ)-induced diabetic rats and mice (Hajiaghaalipour et al., 2015).

The ability of phytochemicals to inhibit AGEs formation is commonly measured using a relatively simple in vitro assay in which bovine serum albumin (BSA) is incubated with glucose or fructose for several days to let glycation proceed, either in the presence or absence of inhibitors (MacPherson et al., 1988; Kim & Kim, 2003). After separation of the proteins from the sugars by dialysis, the amount of AGEs formed can be established by fluorescence

spectrometry or by more advanced analytical techniques such as GC-MS, HPLC, ELISA, western blotting, or immunohistochemistry. The effect of several glycation inhibitors has also been established *in vivo*, using STZ-induced diabetic rats and mice (Xie & Chen, 2013).

Vitamin B derivatives pyridoxamine (**13**) and benfotiamine (**14**) (Fig. 5), and the antioxidant vitamins C (**15**) and E (**16**) showed promising AGE inhibiting activity in preclinical studies, though clinical trials have been rather disappointing so far (Peyroux & Sternberg, 2006). A wide range of flavonoids has been tested for the AGEs inhibiting activity, and a structure-activity comparison indicated that particularly C3-methoxylated flavone aglycones (**17**) show a good promise (Xie & Chen, 2013).

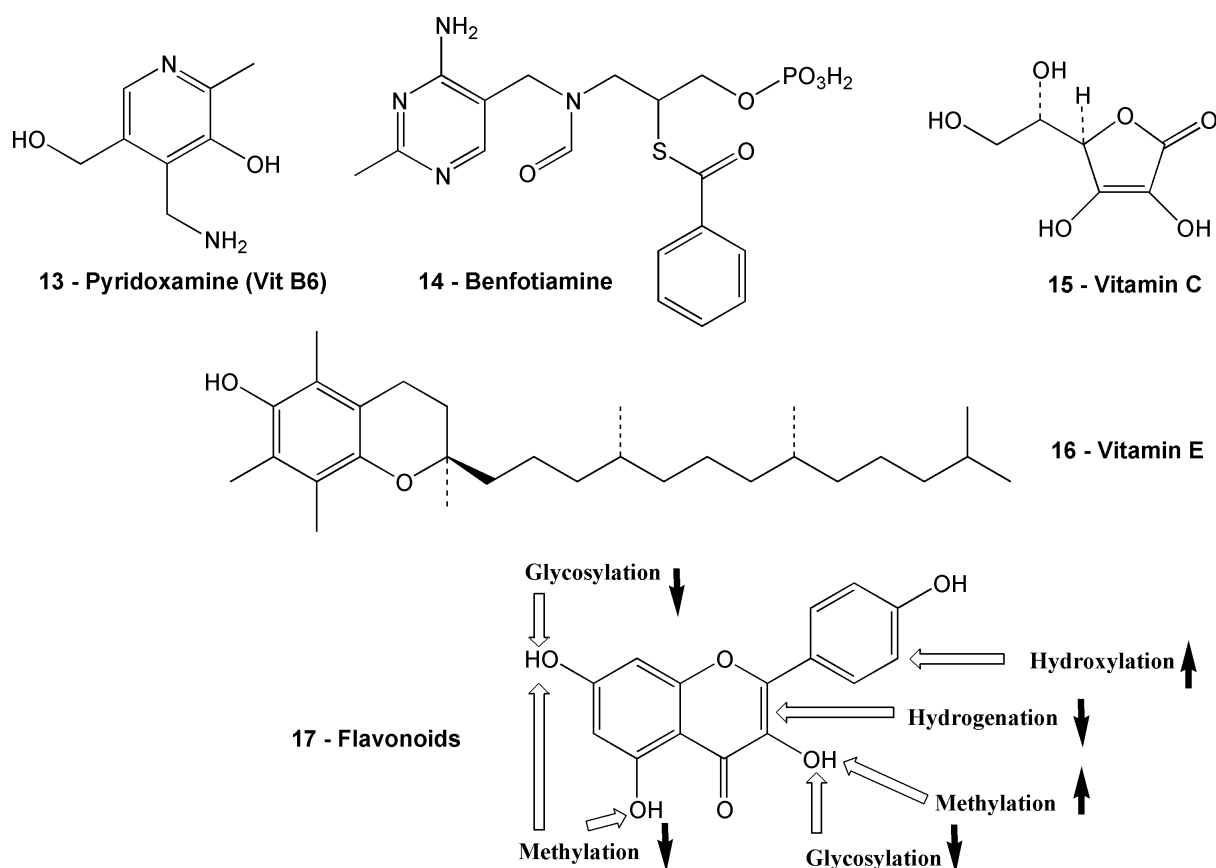


Fig. 5: Inhibitors of AGE formation

The activation of pro-inflammatory signalling pathways by AGEs (Yeh et al., 2017a) can be counteracted by the activation of anti-inflammatory signalling pathways through induction of

transcription factor Nrf2. Best known as the transcription factor reducing oxidative stress, Nrf2 is now recognized for alleviating various causes of stress including xenobiotics, excessive nutrient /metabolite supply, inflammation or accumulation of misfolded proteins. Several modes of Nrf2 activation by phytochemicals have excellently reviewed recently (Matzinger et al., 2018). Most Nrf2-activators have been identified using mammalian in vitro cell cultures. Prominent phytochemical activators of Nrf2-signalling (Fig. 6) include

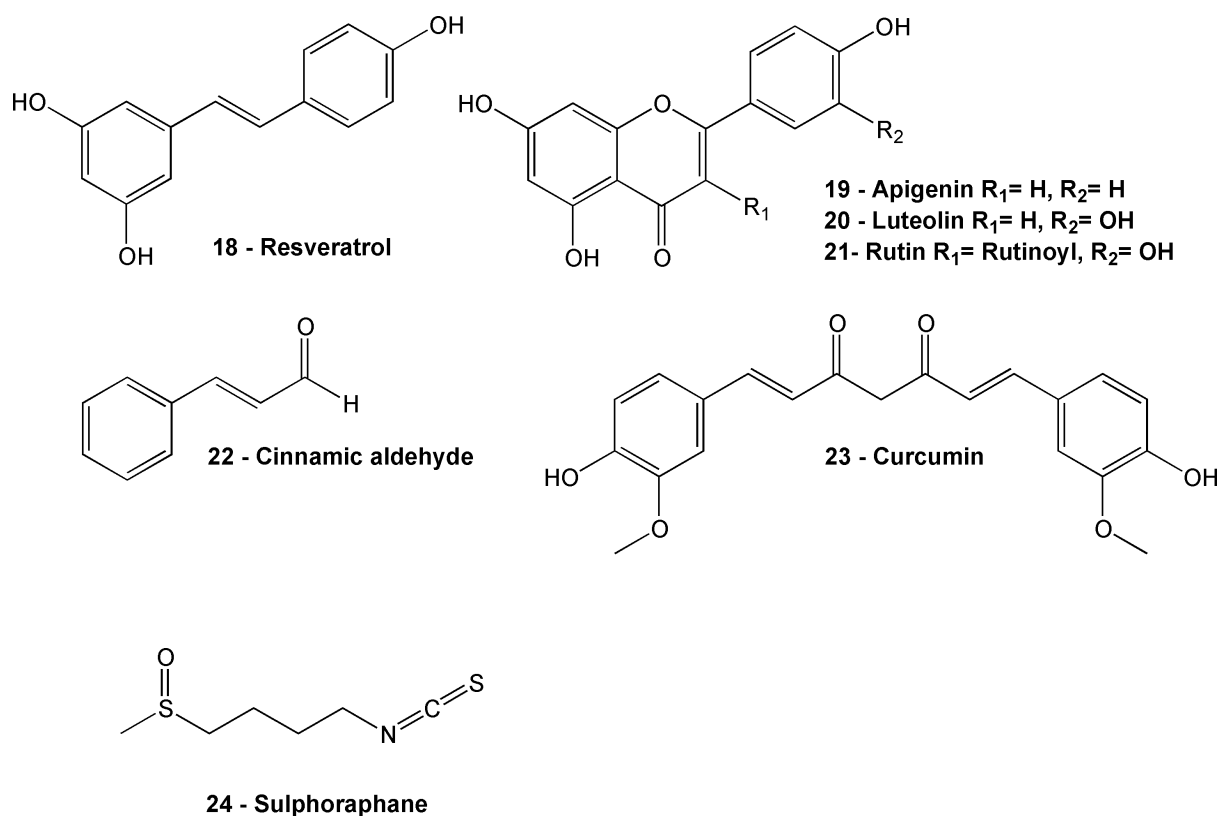


Fig. 6: Activators of Nrf2

resveratrol (**18**), flavonoids - e.g. apigenin (**19**), luteolin (**20**), rutin (**21**), and catechins (**11**, **12**), and other natural compound groups e.g. cinnamic aldehyde (**22**), curcumin (**23**), sulphoraphane (Matzinger et al., 2018). In a similar fashion, palmitate-induced activation of pro-inflammatory signalling pathways in human aortic endothelial cells (HAECs) could be reversed. This time, anthocyanins (**10**) themselves had little effect, but anthocyanin-derived metabolites (**29-31**) attenuated the damaging effects, even at sub-micromolar concentrations

that are known to circulate in humans following blueberry consumption (Bharat et al., 2017). Relief of inflammation and oxidative stress is believed to allow partial restoration of the β -cells in the islets of Langerhans, and may thus indirectly contribute to increased insulin production and consequently to improved glucose homeostasis. In addition, reduction in oxidative stress correlates with reduction in most diabetic complications (Sun et al., 2020).

Bioavailability

In most in vitro bio-assays discussed so far, variable dietary phytochemicals were tested either as aglycones or as the naturally occurring glycosides. The assay results do not necessarily reflect what happens in vivo, because the compounds that are active in the target tissues (e.g. liver, pancreas, kidneys, adipose tissue) are metabolites of the dietary compounds in the form of glutathione, sulfate, or glucuronate conjugates. Of all the naturally occurring glycosides, only glucosides are hydrolysed in the small intestine and subsequently absorbed as aglycones. After absorption, the aglycones are rapidly re-conjugated and enter plasma and the circulatory system; a substantial part of the conjugated molecules is taken out the circulatory system in the liver as then returned into the digestive tract with bile. Other naturally occurring glycosides (e.g. galactosides, rhamnosides, rutinosides) are not absorbed at all, and in an unaltered state enter the large intestine where they are degraded by the intestinal microflora. The bacterial degradation products of dietary compounds are finally absorbed at the very distal end of the human digestive tract. These are the compounds that are ultimately available to assert their activity in the various target tissues, e.g. blueberry anthocyanins malvidin-3-glucoside (**25**) and cyanidin-3-glucoside (**26**) are broken down into the blueberry metabolites hippuric acid (**27**), hydroxyhippuric acid (**28**), benzoic acid-4-

sulfate (**29**), vanillic acid-4-sulfate (**30**), and isovanillic acid-3-sulfate (**31**) (Fig. 7) (Bharat et al., 2017).

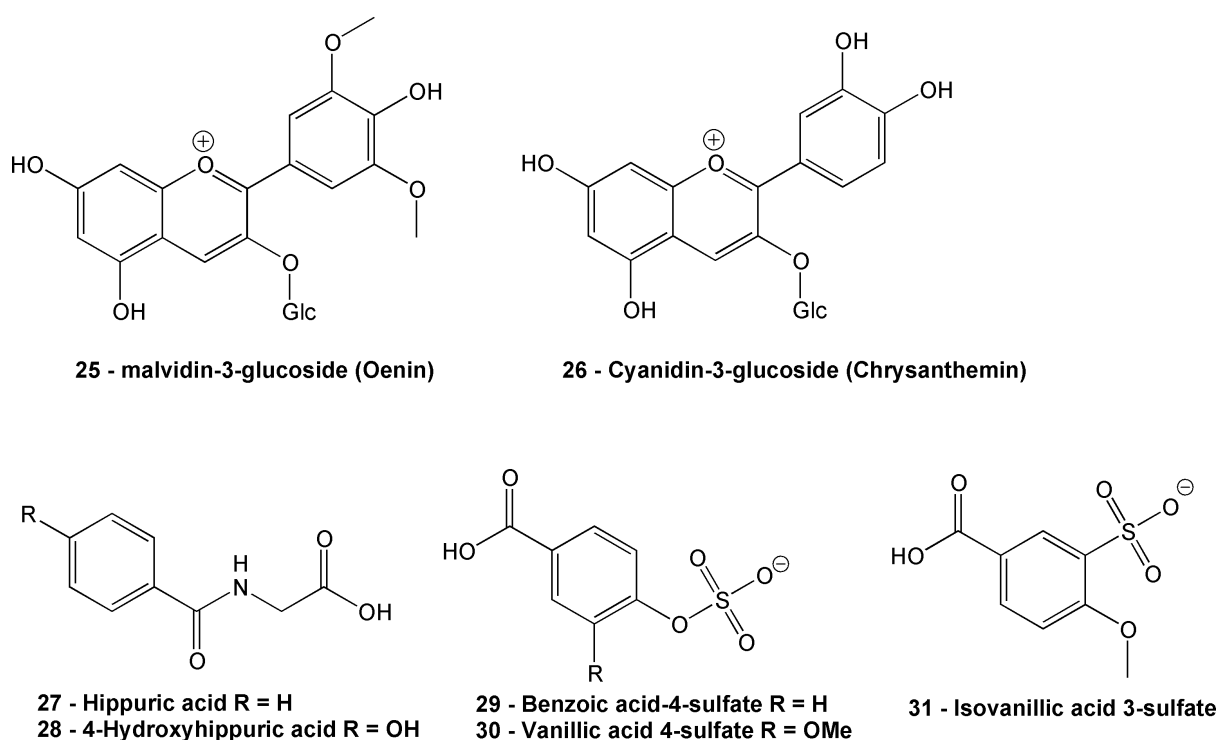


Fig. 7: Anthocyanidins and their metabolites can induce relief of inflammation and oxidative stress

For anthocyanins and other bioactive compounds in food, there is a high inter and intra-individual variation in the response to intake, and a variation in gut microbiota, that in many cases leads to contradictory results in human trials (Eker et al., 2020). In addition, hyperglycaemia, or complications linked with hyperglycaemia, are known to affect bioavailability of phytochemicals (Chen et al., 2017; Wang et al., 2012; Xiao and Högger, 2014; Xie et al., 2012). The understanding on how diabetic condition impacts on the bioavailability of polyphenols is very limited and mainly derives from in vitro and animal studies. The altered pharmacokinetics of polyphenols in diabetics is partly attributed to diabetes-associated malfunctions of liver and/or kidney characterised by modified intestinal β -glucuronidase activity and altered expression of metabolic enzymes as compared to non-diabetics (Lee et al., 2009; Xiao and Högger, 2014). Diabetes-induced changes in the gut

microbiota may further add to the complexity of diabetic influences on the metabolism of polyphenols (Deng et al., 2007; Deng et al., 2008). Hyperglycaemia in diabetics also affects polyphenols' interactions with plasma proteins. Glucose competes with polyphenols for binding to plasma proteins (Wang et al., 2012; Du et al., 2013), and the glycated plasma proteins have weakened non-covalent interaction affinities for dietary phytochemicals (Xie et al., 2012). T2D plasma proteins were found to have up to 10 times lower affinities for polyphenols than healthy human plasma proteins (Xie et al., 2012). Moreover, polyphenols in the blood of diabetics are more inclined to interact with free radicals in plasma. As a consequence, the delivery of polyphenols to other tissues is affected which limits the exploitation of their antioxidant potential (Cao et al. 2015).

Human intervention studies

Studies using whole food - berries

Evidence on effects of consumption of fresh berries on management of the diabetic condition in humans is scarce. One study found that an acute oral dose of 40 g of sweetened dried cranberries (*Vaccinium macrocarpon* Aiton) to T2D adults, in 4 hours resulted in a decreased postprandial level of blood glucose compared to the group fed with an equicaloric amount of white bread (Wilson, 2010). Similar effects on diabetic control have been reported when using processed forms of berries including (freeze) dried, frozen and juiced. Dried cranberries, when taken at 40 g with a high-fat fast-food-style breakfast in an acute setting by T2D patients, led to significant reductions of 16% and 14% in postprandial glucose at 2h and 4h respectively (Schell et al., 2017). The study intervention groups also experienced decreased levels of inflammatory and oxidative stress markers, i.e. interleukin 18 (IL-18) and lipid peroxidation products within the 4h of post-consumption as well. Yet, the chronic

Table 1: Human intervention studies investigating effects of whole food consumption on diabetic and inflammatory markers, antioxidant status and vascular endothelial function in T2D patients

Intervention group	Study design	Dose; duration	Study outcomes (significant)	Reference
13 medicated T2D patients	Randomised, single-crossover, acute, controlled study	55g raw cranberry (RC), 40 g sweetened dried cranberries (SDC), 40 g reduced-sugar dried cranberries (RSDC), 57 g white bread (WB); once	Persisted plasma glucose elevation in WB comparing to other groups. Insulin AUC values for RC and RSDC lower than WB or SDC. Plasma insulin for RSDC lower at 60 min than either WB or SDC.	Wilson et al. (2010)
25 medicated T2D patients	Randomised, crossover, parallel-arm, acute, controlled study	40 g dried cranberries (DC) with high-fat-fast-food-style breakfast (974 kcal), 80 g banana; once	Decreased plasma glucose at 2h and 4h in DC versus banana group.	Schell et al. (2017)
25 medicated T2D patients	Randomised, 2-phase crossover, controlled study	Phase I: 250 g frozen raspberries (FR), 85 g ripe banana (RB); once. Phase II: 250 g FR, 85 g RB; daily for 4 weeks	Phase I: In FR, lower levels of serum glucose at 2 and 4 h postprandial versus control group; levels of inflammatory markers IL-6 and hsTNF- α were also lower at 4 h postprandial in FR versus RB. Phase II: continued lowering effects of FR on lowering IL-6 and hsTNF- α levels versus RB.	Schell et al. (2019)
36 unmedicated T2D patients	Randomised, double-blind, parallel-arm, acute, controlled study	50 g freeze-dried strawberries (FDS), macronutrient matched placebo powder with strawberry flavour (PP); daily for 6 weeks	FDS decreased C-reactive protein levels as a biomarker of inflammation and lipid peroxidation in the form of MDA (lipid peroxidation marker) at 6 weeks versus PP. FDS led to a reduction of HbA1c levels and an increase in total antioxidant status versus PP.	Moazen et al. (2013)
58 T2D patients	Randomised, double-blind, parallel-arm, controlled study	1 cup (240 ml) Cranberry juice (CJ), 240 mL placebo drink (natural mineral water with strawberry flavour) (PD); daily for 12 weeks	At 12 weeks, decreased levels of serum glucose and apo B and increased levels of serum apo A-1 and Paraoxonase-1 (PON-1) activity in CJ compared to their initial values and also with PD.	Shidfar et al. (2012b)
42 medicated T2D patients	Randomised, parallel-arm, controlled study	200 mL barberry juice (BJ), control with no intervention; daily for 8 weeks	After intervention, SBP, DBP, FBS, TC and TG levels decreased and PON-1 as an antioxidant enzyme increased in BJ versus control.	Lazavi et al. (2018)

10 T2D patients for feasibility study (FS). 41 medicated T2D patients for efficacy study (ES).	Randomised, double-blind, controlled study	FS: cocoa drinks containing 75 mg, 371 mg or 963 mg of flavanols; once. ES: 3 doses of cocoa drink (CD-ES) containing 321 mg flavanols per dose daily; 30 days.	FS: A single ingestion of flavanol-containing cocoa was dose-dependently associated with significant acute increases in circulating flavanols and flow-mediated dilation (FMD) of the brachial artery assessed as the vascular function. ES: CD-ES consumption increased baseline FMD by 30% , the acute increases of FMD continued to be manifest throughout the study.	Balzer et al. (2008)
10 T2D patients	Randomised, double-blind, crossover, controlled study	13.5 g high-polyphenol (PL) chocolate (containing 3.5% PL) (HPC), 13.5 g low-PL chocolate containing 0.9% PL (LPC); once	Improvement in endothelial function and decreased oxidative stress measured as the level of urinary 15-F2t-isoprostane in HPC versus LPC.	Mellor et al. (2012)
11 overweight and non-insulin treated T2D patients	A single-dose intervention study	25 mL / day extra-virgin olive oil (EVOO) containing 577 mg of phenolic compounds / kg; 4 weeks	Reduced levels of fasting plasma glucose, HbA1c, aspartate aminotransferase, alanine aminotransferase and visfatin as well as reduced BMI and body weight in EVOO	Santangelo et al. (2016)
80 T2D patients	Randomised, double-blind, controlled study	226.8 mg Brazilian green propolis (BGP), the placebo; daily for 8 weeks	Values of blood uric acid and estimated glomerular filtration rate in patients taking the placebo became worse at 8 weeks compared to the baseline, yet this did not occur in patients consuming BGP.	Fukuda et al. (2012)

effects of berry consumption still remain to be tested in an appropriate study setting. Frozen raspberries (*Rubus idaeus* L.) also show positive impacts on diabetic conditions. An acute feed of frozen raspberries yielded significantly lower levels of blood glucose and inflammatory markers, including IL-6 and high-sensitivity tumour necrosis factor alpha (hsTNF- α), within 4h of postprandial phase. These anti-inflammatory effects of raspberries persisted throughout a continued 4-week supplementation (Schell et al., 2019). In another case, strawberries (*Fragaria x ananassa* Duchesne) in their freeze-dried form taken as a 50 g dose (equiv. to 500 g of fresh strawberries) significantly improved both inflammatory and antioxidant status of subjects with T2D, as indicated by decreased C-reactive protein and lipid peroxidation product levels respectively, after a 6-week supplementation (Moazen et al. 2013). In addition, the intervention also led to a significant reduction in HbA1C, the marker for monitoring of glycemic management (Tanaka et al., 2011). The observed benefits of berries and their processed products in diabetic management are ascribed to their phytochemical content, predominantly anthocyanins (USDA, 2014). The clinical evidence indicates that these flavonoids have potential as adjuvants for the amelioration of diabetic conditions. When consumed in juice form, berries still deliver anti-diabetic effects in T2D adults. In a 12-week randomised and controlled trial, T2D patients who consumed one-cup (240 mL) of cranberry juice daily had decreased levels of fasting blood glucose at week 12 (Shidfar et al., 2012b). Similar results were reported in a barberry (*Berberis vulgaris* L.) juice study, where a daily dose of 200 mL for 8 weeks significantly improved the systolic and diastolic blood pressure, fasting blood sugar as well as blood lipid profiles, including total cholesterol and triglycerides in T2D patients (Lazavi et al., 2018).

Table 2: Human intervention studies investigating effects of tea consumption on diabetic and inflammatory markers, weight status and vascular function in T2D patients

Intervention group	Study design	Dose; duration	Study outcomes (significant)	Reference
16 obese, insulin-resistant males	Randomised, controlled, cross-over study	100 ml black tea (BT), 100 mL beetroot juice (BJ), 100 mL control (water); once	BT decreased vascular resistance (VR) compared to control in conduit, resistance and micro-vessels. BJ decreased postprandial VR in resistance vessels, but not in conduit artery and micro-vessels. Postprandial insulin response was attenuated by ~29 % after tea, but not beetroot juice.	Fuchs et al. (2016)
50 T2D patients	Randomised, double-blind, controlled study	3 cups (600 mL) Diabetea tea™ extract (DT), 3 cups (600 mL) placebo extract (PL); daily for 12 weeks	DT suppressed CD4+ T cell expression of IL-1 beta and IL-8 and up-regulated the expression of IL-10 and the Treg/IL-17 ratio. A significant decrease in HbA1c and LDL was observed at the end of the study period in DT.	Mahmoud et al. (2016)
16 T2D patients	Randomised, controlled, cross-over study	6 g <i>Gynostemma pentaphyllum</i> (GP) tea, 6 g placebo green tea (PGT); daily for 4 weeks	The FBG and steady-state plasma glucose were lower after GP treatment compared to PGT treatment. The levels of FPG in PGT group were slightly reduced to 0.2 +/- 1.5 versus 1.9 +/- 1.0 mmol/L in GP group.	Huyen et al. (2013)

43 non-insulin treated T2D patients	Randomised, double-blind, parallel-arm, controlled study	Green tea containing 582.8 mg of catechins (catechin group), green tea containing 96.3 mg of catechins (control group); daily for 12 weeks.	The decrease in waist circumference was greater in the catechin group versus control group. Adiponectin, which is negatively correlated with visceral adiposity, increased only in the catechin group. The increase in plasma insulin (Ins) at week 12 was greater in the catechin group than in the control group. In patients treated with insulinotropic agents, the increase in insulin levels was observed only in the catechin group, and the decrease in HbA1c at week 12 was greater in the catechin group than in the control group.	Nagao et al. 2009
63 T2D patients	Randomized, parallel, controlled study	4 cups of green tea (4C), 2 cups of green tea (2C), no green tea (0C); daily for two months.	4C had a decrease in body weight, BMI, waist circumference, and SBP.	Mousavi et al. 2013
55 T2D patients	Randomised, crossover, controlled study	9g green tea contained in 900 mL water, control; daily for 4 weeks.	Inflammatory markers, such as hsCRP and IL-6, blood glucose, lipid profiles, insulin resistance, serum adiponectin levels, brachial-ankle pulse wave velocity were unchanged after green tea consumption.	Ryu et al. 2006

100 T2D patients

Randomized,
parallel study

150 mL Sour tea (ST), 150 mL green
tea (GT); three times a day for 4
weeks.

HDL-c increased in both groups. The
median of FBI in GT showed a decrease
unlike the ST which showed an increase.
The median of HOMA-IR after the
intervention in GT showed lower levels
than the ST. The median of b% only in ST
showed increase after the intervention.
The mean of S% only in ST showed a
decrease after the intervention.

Mozaffari-Khosravi
et al. [2014a](#)

Further studies using whole food - Cocoa-beans, virgin olive oil, propolis

Cocoa (*Theobroma cacao* L.) -based food products have been found owning therapeutic potential in reducing the risk of vascular dysfunction among medicated diabetic patients. An acute consumption of cocoa powder-formulated drinks rich in flavanols, predominantly epicatechins (**11-12**), caused a significant improvement in the vascular endothelial function of medicated T2D patients (Balzer et al., 2008). The effects went in a dose-dependent manner when cocoa drinks containing flavanol contents of 75 mg, 371 mg and 963 mg were applied sequentially to the patients on 3 separate occasions (Balzer et al., 2008). The cardioprotective benefits of the cocoa drinks were also testified at a flavanol content level of 321 mg per dose in a 30-day intervention with 3 doses ingested daily, following the acute study (Balzer et al., 2008). Similar acute effects of cocoa on vascular endothelial health were manifested in the form of high-polyphenol contained (3.5% w/w) chocolate after a 2h consumption among T2D patients with or without medication. In addition, the protective role of the flavanol-rich chocolate against the acute hyperglycaemia-induced oxidative stress were also shown in those patients (Mellor et al., 2012). Epicatechins (**11-12**), as the predominant form of polyphenols found in cocoa-based food and beverages, have been suggested be responsible for the anti-diabetic outcomes, due to their known properties of improving the serum antioxidative status and increasing nitric oxide levels via its modulation on nitric oxide synthase (Hollman et al., 2011). Periodic hyperglycaemia as a common feature of diabetes can cause an increased level of oxidative stress, which can then deteriorate the vascular endothelial functions (Brownlee, 2001). This may partly account how phytochemical antioxidants deliver merits to the anti-diabetic battles.

Extra-virgin olive oil, pressed from the fruits of *Olea europaea* L., and commonly consumed as part of the Mediterranean diet, has drawn considerable interest for its benefits in controlling diabetic conditions. In a 4-week intervention study, overweight T2D patients

Table 3: Human intervention studies investigating effects of fruit extract consumption on diabetic markers and antioxidant status in T2D patients

Intervention group	Study design	Dose; duration	Study outcomes (significant)	Reference
37 T2D patients resistant to conventional oral anti-hyperglycaemic drugs	Randomised, double-blind, controlled study	A capsule of 350 mg whortleberry fruit extract, placebo; every 8h for 2 months	The extract lowered the levels of FBG, 2-h postprandial glucose, and HbA1c (p = 0.007, p 0.05) versus placebo after the intervention.	Kianbakht et al. 2013
13 T2D patients	Randomised, double-blind, controlled study	1 mg <i>Berberis</i> fruit extract (BFE), placebo; twice daily for 2 months	BFE had a reduction in serum glucose and HbA1c levels during the 8 weeks of study.	Moazezi & Qujeq (2014)
31 T2D patients	Randomised, double-blind, controlled study	3 g/d <i>Berberis vulgaris</i> fruit extract (BVFE), placebo; 3 months	There were decreases in serum TG, TC, LDL-c, apo B, glucose, and insulin and a significant increase in TAC at the end of the study in BVFE versus placebo. There were differences in serum TG, TC, LDL-c, apoB, glucose, insulin, TAC, and insulin resistance between the two groups at the end of the study.	Shidfar et al. (2012a)
60 T2D patients	Randomised, double-blind, controlled study	A capsule of <i>Cornus mas</i> L. fruit extract (FE) containing 150 mg anthocyanins; placebo; 2 capsules twice daily for 6 weeks	The insulin level increased while the HbA1C and TG levels decreased in FE versus placebo.	Soltani et al. (2015)
8 male T2D patients	Randomised, crossover, acute, controlled study	0.47 g standardised bilberry extract (BE) (36 % (w/w) anthocyanins) which equates to about 50 g of fresh bilberries, placebo; once	BE had a significant decrease in the incremental AUC for both glucose and insulin versus placebo.	Hoggard et al. 2013

49 T2D patients	Randomised, double-blind, placebo-controlled, multiple-dose study	375 mg capsule containing 150 mg of green tea catechins (equivalent to the amount in 7 cups of green tea) and 75 mg of black tea theaflavins (equivalent to the amount in 35 cups of black tea), 375 mg capsule of cellulose; daily for 3 months	The changes in glycosylated hemoglobin were not significantly different between study arms. No hypoglycemic effect of extract of green or black tea was found.	Mackenzie et al. 2007
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showed significantly improved glycaemic control status, body mass index (BMI) and circulating profile of inflammatory adipocytokines after a daily consumption of high-polyphenol extra virgin olive oil containing 577 mg of phenolic compounds/kg (Santangelo et al., 2016).

Another type of food, Brazilian green propolis which is less commonly consumed compared to the foods aforementioned, was studied in an 8-week feeding trial. T2D adults who received 226.8 mg/day of the propolis did not show significant improvement of the hyperglycaemic state, but the treatment prevented a reduction of glomerular filtration rate and concomitant build-up of uric acid that is commonly seen in T2D patients (Fukuda et al., 2015).

Beverage consumption - Black tea

In addition to fruit juice, several research studies paid attention to tea (*Camellia sinensis* (L.) Kuntze), one of the most commonly consumed beverages in the world, and regarded its anti-diabetic functions. Ingestion of 100 mL of flavonoid-rich black tea resulted in decreased peripheral vascular resistance (VR) and an attenuation of postprandial insulin response by approximately 29% among a group of obese and insulin-resistant male adults within 3h after consumption (Fuchs et al., 2016). Beet juice, pressed from the taproot of *Beta vulgaris* L., is rich in nitrate and a dietary source of nitric oxide (Lundberg et al., 2006), was tested in the same study group at a level of 100 mL, but exerted less modulating impact on the postprandial skeletal blood flow and glucose homeostasis compared to black tea. It indicated that the effects of black tea may be ascribed to its flavonoid content that has the potential of improving vascular endothelial functions (Ras et al., 2011), which can then stimulate the postprandial blood flow responses (Fuchs et al., 2016). The anti-diabetic efficacy of black tea was also examined when taken in a mixed formula with other types of medicinal plants. Diabetea teaTM, a type of herbal tea with its main constituent being black tea (60% w/w) and

Table 4: Human intervention studies investigating effects of the consumption of herb and spice extract on diabetic and inflammatory markers and antioxidant status in T2D patients

Intervention group	Study design	Dose; duration	Study outcomes (significant data)	Reference
19 well-controlled T2D patients	Randomised, double-blind, crossover, acute, controlled study	A capsule of 6 g <i>Panax ginseng</i> , placebo (vanilla-flavoured capsulated corn starch); daily for 12 weeks	Decreased 75 g-OGTT-PG indices, fasting-PI and 75 g-OGTT-PI indices, and increased fasting-ISI (HOMA) and 75 g-OGTT-ISI versus placebo.	Vuksan et al. 2008
20 T2D patients	Randomised, crossover, controlled study	2.2 g <i>Panax ginseng</i> root in capsules, placebo; daily for 4 weeks	Great decrease in HOMA-IR after ginseng intervention. Lower fasting plasma glucose in ginseng group versus placebo group.	Ma et al. 2008
9 T2D patients	Randomised, controlled study	3-g American Ginseng (AG) capsules, placebo; once	Differences found in postprandial glycaemia between AG and placebo when capsules were taken 40 min before or together with 25 g oral glucose challenge	Vuksan et al. 2000a
10 T2D patients	Randomised, acute, controlled study	3, 6, or 9 g ground American Ginseng (AG) root in capsules, 0 g (placebo); once	Treatment (0, 3, 6, and 9 g AG) affected postprandial glycaemia. compared with 0 g (placebo). Either dose of AG reduced AUC and incremental glycemia at 30 min, 45 min and 120 min respectively.	Vuksan et al. 2000b
41 T2D patients	Randomized, double-blind, placebo-controlled	2 g/day of ginger powder (GP) supplement, lactose as placebo (LP); 12 weeks	Reduced levels of FBG, HbA1c, apo B, apo B/apo A-I and MDA in GP after intervention in comparison to their baseline and LP. The level of apolipoprotein A-I increased in GP.	Khandouzi et al. (2015)

88 T2D patients	Randomized, double-blind, placebo-controlled study	3 one-gram capsules containing ginger powder (GP), 3 one-gram control capsules; daily for 8 weeks	FBG mean showed a decrease in ginger, whereas control had an increase. Similar variation found in HbA1c. Differences found in the median of fasting insulin level, IS% and HOMA-IR between GP and control before and after the intervention. QUICKI mean increased more in GP after intervention versus control.	Mozaffari-Khosravi et al. (2014b)
204 T2D patients	Randomized, single-blind, parallel, controlled study	3 g ginger dried powder (GDP), control; daily for 8 weeks	GDP had beneficial effects on TC, LDL, and HDL levels versus control.	Azimi et al. (2014)
40 T2D patients	Randomized, double-blind, placebo-controlled study	3 g of <i>Momordica charantia</i> fruit and seed extract in capsules, placebo; 3 months	No significant change in HbA1c or FBG values.	Dans et al. (2007)
51 T2D patients	Randomized, double-blind, placebo-controlled study	6 g of <i>Momordica charantia</i> fruit and seed extract in capsules, placebo; 1 month	No significant change in HbA1c or FBG values.	John et al. (2003)
51 T2D patients	Randomized, placebo-controlled study	1, 3, or 6 g cinnamon daily, respectively, placebo; 40 days	All three levels of cinnamon reduced the mean FBG, TG, LDL and TC levels	Khan et al. (2003)
79 T2D patients	Randomized, double-blind, placebo-controlled study	3 g a cinnamon extract powder (CE), a placebo capsule (PC); three times a day for 4 months	Higher reduction of FBG in CE than PC between pre- and post-intervention	Mang et al. (2006)
42 T2D patients	Randomized, double-blind, placebo-controlled study	500 mg cinnamon (<i>C. cassia</i>) in a capsule, 500 mg placebo (wheat flour) in a capsule; twice daily for 3 months	No significant differences between the cinnamon and placebo groups in the change in any measure of FBG, TC, LDL, HDL, TG and insulin levels from baseline to 3 months	Blevins et al. (2007)
204 T2D patients	Randomized, single-blind, parallel, controlled study	3 g cinnamon dried powder (CDP), control; daily for 8 weeks	CDP had beneficial effects on TC, LDL, and HDL levels versus control.	Azimi et al. (2014)

60 T2D patients on metformin therapy

Randomized, placebo-controlled study

2 g turmeric supplements (TS); control with no treatment; daily for 4 weeks

Decreased FBG and HbA1c levels, an reduction in MDA and hsCRP (inflammatory marker) levels, and enhanced total antioxidant status in TS versus control. TS had improved lipid metabolism shown in the levels of LDL, non-HDL cholesterol and LDL/HDL ratio.

Maithili Karpaga Selvi et al. (2015)

the remaining comprising 12 other ground dried medicinal herbs, was given to medicated T2D patients at a daily dose of 3 cups (equiv. 7.5g dry tea) for a period of 12 weeks (Mahmoud et al., 2016). Positive results were seen as a significant reduction of the concentration of HbA1c and low-density lipoprotein (LDL), and also a suppression of inflammatory markers among patients. It was suggested that flavonoids, triterpenes and phytosterol contents contribute to the anti-diabetic properties of the tea. Another type of herbal tea called Jiaogulan (*Gynostemma pentaphyllum* Thunb.) tea demonstrated a capacity of reducing the fasting plasma glucose level and improving the insulin sensitivity in T2D patients when consumed at 6 g daily for 4 weeks (Huyen et al., 2013). Jiaogulan is a wild herb native to China and Vietnam, where it has been widely used as a medicinal herb for prevention and amelioration of diabetes. The potential of glycaemic control of this herb in T2D, is suggested be attributed to its dammarane-type triterpenoids (**32**) (Fig. 8) (Huyen et al., 2010; Huyen et al., 2012). To date, limited studies have examined the effects of green tea in diabetic management, yet study outcomes appear to be mixed in the current evidence. In the study on the Jiaogulan herbal tea (Huyen et al., 2013), green tea (*Camellia sinensis* (L.) Kunze) was used as the placebo consumed at a dose of 6 g for 4 weeks. However, the latter exerted fewer effects on the fasting blood glucose status and also yielded a lower level of insulin sensitivity measured by the values of the steady-state-plasma. In a study among T2D patients, a six-fold increment in the ingestion dose of catechins (**11-12**) (from 96.3 mg to 582.8 mg daily) delivered as green tea led to significantly greater reductions in both waist circumference and HbA1c levels after a 12-week intervention, with the latter effect only found in patients receiving insulinotropic agents (Nagao et al. 2009). In general, there was no significant difference in plasma glucose and HbA1c between the two groups. Besides, the

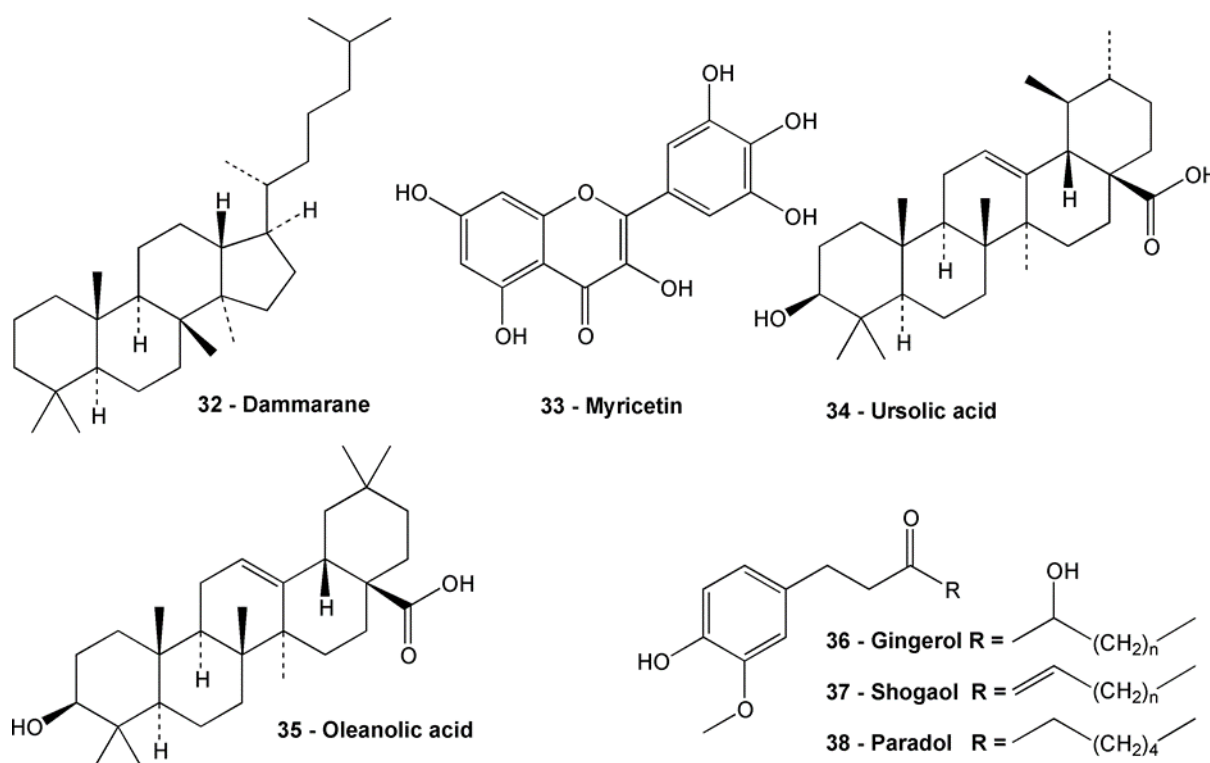


Fig. 8: Phytochemicals from cornelian cherry (*Cornus spec.*), ginseng and ginger can restore glucose homeostasis

only significant increases in serum insulin and adiponectin that is negatively linked to visceral adiposity were observed in the higher-catechin-dosed group only (Nagao et al., 2009). This represents the potential of using green tea as an agent for HbA1c-control and weight management for T2D patients. The benefits of green tea on weight control was also found among T2D patients when ingested with four cups of green tea (prepared using 2.5 g tea bags in 200 mL of boiling water) for a period of 2 months. In addition, a reduction in systolic blood pressure also appeared post intervention. However, no effects were detected on glucose metabolic and oxidative stress markers (Mousavi et al., 2013). Catechins were suggested the main player for improving the anthropometric measures of patients (Nagao et al., 2007; Chantre et al., 2002). Similarly, green tea seemed to be ineffective in modulating the inflammatory status and arterial stiffness among T2D participants after their consumption of 9 g of green tea infused in 900 mL of water daily for 4 weeks (Ryu et al. 2006). Green tea,

when compared to sour tea (*Hibiscus sabdariffa* L.), showed a better outcome in lowering the level of insulin resistance measured by homeostasis model assessment of insulin resistance among T2D patients at an ingested dose of 3g / tea bag in 150 mL of hot water for 3 times a day over 4 weeks (Mozaffari-Khosravi et al. 2014). Based on the evidence above, the anti-diabetic effect of green tea remains inconclusive and requires further exploration.

Plant food extracts

The antidiabetic effects of phytochemicals are not limited to whole foods, but also evidenced in studies using fruit extracts as the intervention foods. Caucasian whortleberry (*Vaccinium arctostaphylos* L.) was examined in an intervention study testing its efficacy of glycaemic control in T2D patients who were resistant to conventional anti-hyperglycaemic drugs (Kianbakht et al. 2013). 350 mg of the whortleberry fruit hydroalcoholic extract was delivered in a form of capsule containing excipient weighted at 19.2% w/w to patients for every 8h for 2 months in combination with anti-hyperglycaemic drugs. The result was a significant reduction of fasting blood glucose, 2h-postprandial glucose and HbA1c levels in patients. The safety of its consumption was also testified. Thus, whortleberry fruits were shown to exert safe and beneficial effects in enhancing glycaemic control to a greater extent than using anti-hyperglycaemic drugs solely in diabetic patients (Kianbakht et al. 2013). Anthocyanins (**10**) were supposed to account for the anti-glycaemic action (Kianbakht et al. 2013). Apart from anthocyanins, whortleberries are also known to contain chlorogenic acid (**7**) (Abidov et al. 2006) and myricetin (**33**) (Fig. 8) (Ayaz et al. 2005), which might potentially contribute to the glycaemic control capacity of the fruits (van Dijk et al. 2009; Ong et al. 2000). In a study of the similar research setting involving T2D patients who went on a 2-month intervention with 1 mg of barberry (*Berberis* fruit) extract supplementation delivered in a capsule twice daily (Moazezi and Qujeq, 2014). The barberry fruit extract

exhibited noticeable effects on glucose metabolism regulation in patients who experienced significantly reduced serum glucose and HbA1c levels post intervention (Moazezi and Qujeq, 2014). Besides, Shidfar et al. (2012a) also revealed the potential of barberry extract on improving blood lipid profile favourable to cardiovascular health, enhancing the Total Antioxidant Capacity and improving the glucose metabolism of T2D patients using a higher dose at 3 g/d for a duration of 3 months (Shidfar et al. 2012a). The mechanism for those observed effects was suggested be ascribed to the anti-diabetic actions of berberine (**3**) which is the main active alkaloid found in barberry at a content level of 5.2-7.7% (Shidfar et al., 2012a). This notion is also supported by studies using berberine (**3**) on its own ingested at a dose of 500 mg 2-3 times a day for 12-13 weeks among newly diagnosed T2D patients (Yin et al. 2008; Dange et al. 2016). Both studies confirmed the positive modulating effect of berberine (**3**) on glucose and lipid metabolism in patients, which was comparable to that of metformin (**1**). The observed benefits may be attributed to the induction of glycolysis pathway and/or inhibition of the glucosidase enzymes acted by berberine (**3**), as previously suggested by (Yin et al. 2008; Zhang et al. 2008). Another rich source of anthocyanins (**10**), cornelian cherry (*Cornus mas* L.) extract, was tested on 60 T2D patients that took 2 capsules twice daily for 6 weeks, with each capsule containing 150 mg of anthocyanins (**10**). The intervention yielded improvements in glycaemic control reflected by increased insulin level and decreased levels of HbA1c and plasma triglycerides (Soltani et al., 2015). Anthocyanin contents of the fruit may be accountable for the observed effects, based on the previous *in vitro* (Jayaprakasam et al. 2005) and animal studies (Jayaprakasam et al. 2006). In addition, the triterpenoids ursolic acid (**34**) (Zhang et al. 2006) and oleanolic acid (**35**) (Fig. 8) (Hsu et al. 2006), present in the fruit have been given the merit for possibly playing a role in patient's glucose homeostasis together with anthocyanins (**10**). Anti-diabetic properties of plant fruit extract have also been illustrated in an acute setting. Bilberry (*Vaccinium myrtillus* L.) extract

as the test food was given to individual T2D patients at a dose of 0.47 g (36% w/w anthocyanins (**10**), equating to about 50 g of fresh bilberries) contained in a single capsule (Hoggard et al. 2013). Mixed results were obtained including significant improvements in postprandial glycaemic response at 120, 150 and 180 minutes post consumption, and no changes were found in examined markers of inflammation and oxidation during the period of 300 min after dosage (Hoggard et al. 2013). The positive impact on lowering glycaemic response may be linked to the actions of the anthocyanin (**10**) contents of the fruit (Cai et al. 2011), typically cyanidin-3-galactoside (**26**) (Adisakwattana et al. 2009) and oligomeric procyanidins (Schäfer and Högger, 2007; Kumar et al. 2011). Those bioactive components have shown the potency of reducing the breakdown of carbohydrates via their inhibitory actions on α -glucosidase *in vitro* (Adisakwattana et al. 2009; Schäfer and Högger, 2007). In contrast to the intervention trials with tea as a beverage (Fuchs et al., 2016), capsules with dried standardised tea extract did not show convincing results in T2D patients (Mackenzie et al. 2007). A mixture of decaffeinated green tea and black tea extract was ingested at two different doses (375 mg and 750 mg in a capsule per day) with each arm lasting for 3 months among T2D patients, 80% of whom being on hypoglycaemic medication. Despite the concentrated polyphenol content of the test capsules, i.e. the 375 mg capsule was constituted of 150 mg of green tea catechins (equating to 7 cups of green tea) and 75 mg of black tea theaflavins (equating to 35 cups of black tea), the glycaemic responses between the test foods and placebo formula did not vary significantly among patients after the intervention (Mackenzie et al. 2007).

Medicinal herbs and spices in a powder form

Apart from the approach of using whole-foods, their extract or beverages, phytochemicals are traded abundantly in the form of ground herbal or spice powders. Ginseng, including both

American ginseng (*Panax quinquefolius* L.) and Asian ginseng (*Panax ginseng* C.A Meyer), has attracted emerging interest for its glycaemic control potency for T2D. *Panax ginseng*, when dosed as capsules at a daily intake level of 6 g per T2D patient for 12 weeks, delivered favourable effects in glycaemic control regarding modulation of plasma glucose and insulin levels for healthy T2D patients. Still, HbA1c level remained unchanged throughout the intervention (Vuksan et al., 2008). The hypoglycaemic and insulin-sensitising effect of *Panax ginseng* was preserved when the ingestion dose dropped to around 2.2 g per day for a shorter intervention period of 4 weeks among well-controlled T2D patients by either habitual diet or hypoglycaemic agents (Ma et al. 2008). Yet, although insulin resistance decreased significantly compared to that observed in the placebo group, the plasma insulin levels remained unaffected, which contrasted with results of a previous study (Vuksan et al., 2008). No effects were shown on oxidative stress and antioxidant capacity markers either (Ma et al., 2008), which might be due to the low level of antioxidant capacity of the supplement used (Ma et al., 2008), as compared to that of other plant foods, i.e. fruits and vegetables and teas when using the same assessment technique, i.e. FRAP assay (Szeto et al., 2002). The active components of ginseng, i.e. ginsenosides - glycosides of dammarane triterpenoids (**32**), were hypothesised to be accountable for the anti-diabetic effects of ginseng supplementation (Sievenpiper et al., 2004). However, due to the large variability among ginsenoside composition of ginseng (Vuksan et al., 2008) and the unknown bioactivity profile of the individual ginsenosides, the mechanistic basis for the clinical observations remains as yet unclear. Two acute intervention studies found that ground American ginseng, when given as a 3g-capsule per person, T2D patients experienced significant reductions in postprandial glycaemia, with the reduction of incremental glycaemia occurring as early as 30 min post-consumption as compared to the placebo group (Vuksan et al., 2000a, b). Again, the ginsenosides were suggested to be the main factor for mediation of the glycaemic response in

patients, but other bioactive components of ginseng including polysaccharides (ginsenosides) and peptidoglycan (panaxans) may also contribute to the global effects of ginseng (Attele et al. 1999). Enhancement of nitric oxide synthesis via the action of ginsenosides (Gillis, 1997) is regarded as one of the plausible mechanistic explanations for the improved insulin sensitivity and carbohydrate metabolism resulted from ginseng supplementation (Roy et al. 1998; Spinas et al. 1998).

Ginger (*Zingiber officinale* Roscoe), as another type of herbal plant, has shown positive effects on regulating glucose homeostasis, improving blood lipid profile and enhancing antioxidant capacity when delivered as ground rhizome powders to T2D patients (Khandouzi et al. 2015; Mozaffari-Khosravi et al. 2014b; Azimi et al. 2014). The tested doses used ranged from 2 g to 3 g per day over an intervention period of 8 or 12 weeks among T2D patients. The reported beneficial effects of ginger supplementation may be attributed to its bioactive and also antioxidant components typically gingerol (**36**), shogaol (**37**) and paradol (**38**) (Fig. 8) (Fuhrman et al. 2000; Lebda et al. 2012). In contrast, a similar dose of bitter melon (*Momordica charantia* L.) fruit and extract ingested to T2D patients at a dose of 3 g or 6 g for either 3 months or 1 month respectively has not given any significant changes in markers of glycaemic control, yet, no side effects were documented (Dans et al. 2007; John et al. 2003). Other common spices have been looked at in studies recruiting different intervention settings. Cinnamon (*Cinnamomum verum* J.Presl.) bark has exerted some extent of glycaemic control in T2D patients with moderate effects shown on fasting blood glucose level only, yet evidence has been mixed among studies using different doses (1g, 3g or 6g) and durations of intervention (40 days, 8 weeks, 4 months or 3 months), as well as recruiting T2D patients at various diabetic management status (Khan et al. 2003; Mang et al. 2006; Blevins et al. 2007; Azimi et al. 2014). Similarly, cinnamon (3g/day), cardamom (*Elettaria cardamomum* (L.) Maton) small seed pods (3g/day) and saffron (*Crocus sativus* L.) stamens

Table 5: Key phytochemicals mentioned in the literature, their modes of action and molecular targets

Compound class	Modes of antidiabetic actions	Molecular target	Type of study	Reference
Catechins	Modulate glucose absorption and uptake, reduce glycaemia. Reduce lipid absorption, regulate lipid profile. Improve insulin resistance.	Pancreatic α -glucosidase, α -amylase and maltase, Na ⁺ -dependent glucose transporter (SGLT1), AMPK activation. Bile acid metabolism and lipogenesis in hepatic cells. JNK-activated signalling pathway, expression of antioxidant genes and PTP1B.	<i>In vitro</i> , animal and human studies	Kim et al., 2013; Kobayashi et al., 2000; Li et al., 2018a; Li et al., 2018b; Mi et al., 2018. Shimizu et al., 2000; Solinas & Becattini, 2016; Tsuneki et al., 2004; Ueda et al., 2010; Zhong et al., 2006.
Anthocyanidins	Inhibition of oxidative stress and reduce blood glucose. Improve insulin resistance, regulate blood lipid profile. Stimulate insulin secretion.	Endogenous antioxidant enzymes and islet β cells. Adipocytes, insulin pathway activation via FoxO1, TNF- α . Expression of intracellular Ca ²⁺ signalling pathway and glucose transport-related gene (Glut2), DPPIV and its substrate GLP-1, mRNA expression of insulin receptor-related genes.	<i>In vitro</i> , animal studies	Roy et al., 2008; Tsuda et al., 1999; Zhu et al., 2012; Yan & Zheng, 2017. Takikawa et al., 2010; Guo et al., 2012. Sun et al., 2018; Johnson & Mejia, 2016.
Proanthocyanidins	Reducing carbohydrate digestion, modulating hepatic glucose metabolism. Modulate Pancreatic β -cell functions. Protecting against diabetic neuropathy.	α -glycosidase. Hepatic glucokinase activity, phosphoenolpyruvate carboxykinase, activation of AMPK and PI3K/Akt pathways to decrease glucose-6-phosphatase, insulin signalling pathways. Oxidative stress, insulin secretion and β -cell survival. Endoplasmic reticulum (ER) stress modulation and pulmonary arteries.	<i>In vitro</i> , animal studies	Johnson, et al., 2013; Lee, et al., 2007; Schafer & Hogger, 2007; Zhang et al., 2009; Bang & Choung, 2014; Cordero-Herrera, et al., 2013; Kurimoto et al., 2013; Yang & Chan, 2017. Ding et al., 2014 ; Pinna et al., 2017.

Procyanidins	Reduce blood glucose and macronutrient digestion. Improve insulin sensitivity, insulin resistance and hepatic gluconeogenesis. Promote glucose homeostasis. Prevent β -cell dysfunction.	Liver lipogenesis, insulin and AMPK signalling pathways' activation for inducing the translocation of GLUT4 in skeletal muscle, intestinal amylases, proteases and lipases. Pro-inflammatory cytokine expression, hepatic inflammation suppression, lipid depot in the adipose tissue and liver. Islet β cell apoptosis prevention, Pdx1 and Glut2 mRNA expression, and antioxidant levels in pancreatic tissue. Hepatic NAD ⁺ biosynthesis	<i>in vitro</i> , animal studies	Cremonini, et al., 2016; Baiges et al., 2010; Lu et al., 2011; Chen et al., 2012; Ahangarpour et al., 2016; Yamashita et al., 2016; Vazquez-Flores et al., 2018.
Stilbenoids	Modulate hepatic glucose metabolism. Improve glucose homeostasis. Promote glucose uptake and intracellular transport. Prevent insulin resistance. Enhance β -cell function and insulin secretion. Antioxidant defence enhancement in pancreatic tissue.	Modulation of glucose and glycogen metabolism enzymes. Glycogen synthase activation and glycogen phosphorylase inhibition, reduced expression of transcription factor NF- κ B and pro-inflammatory cytokines (IL-1 β and IL-6) in liver. Increased number of glucose transporter GLUT4 and its translocation to plasma membrane of myocyte via PI3K-Akt pathway. Fatty acid oxidation promotion, and decreased activity of glucokinase in skeletal muscle. Caspase-3 inhibition for preventing β -cell apoptosis. Activity of antioxidant enzymes (CAT, SOD, GPx, and glutathione-S-transferase).	Animal and human studies	Palsamy & Subramanian, 2009; Andrade et al., 2014; Do et al., 2012; Deng et al., 2008; Tan et al., 2012; Chi et al., 2007; Goh et al., 2014; Chen et al., 2011; Palsamy & Subramanian, 2010;

Tannins	Delay intestinal glucose digestion and absorption, and reduce blood glucose level. Upregulate glucose transport.	Decreased oxidative stress in pancreatic β cells, and α -amylase and α -glucosidase inhibition. Stimulated phosphorylation of protein factors in the insulin-mediated glucose transport pathway.	<i>In vitro</i> , animal and human studies	Serrano et al., 2009; Hosoyama et al., 2003; Zhang & Kashket, 1998; Kato et al., 2017; Matsui et al., 2007; Gin et al., 1999; Liu et al., 2005;
Curcumin	Hypoglycaemic effect, protect β -cell, decrease insulin resistance, regulate lipid metabolism	Mitigated ER stress and oxidative stress via activated Nrf2-Keap1 antioxidant response, decreased adipogenesis and enhanced catabolism of adipotic tissues, AMPK activation and upregulation of fibroblast growth factor 21 (FGF21) amount and/or action.	<i>In vitro</i> , animal and human studies	Jin et al., 2018; Pivari et al., 2019; Rashid et al., 2017; Zha et al., 2018)
Hydroxycinnamic acids	Reduce blood glucose level, improve insulin resistance, increase insulin secretion and sensitivity, improve β -cell function.	Increased glucinase activity, and decreased glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities in liver; modulation of glucose metabolism enzymes, AMP-activated protein kinase activation, inhibition of adipogenesis and gluconeogenesis, protection against glucolipotoxicity-mediated oxidative stress and inflammation.	<i>In vitro</i> , animal studies	Kasetti et al., 2012; Jung et al., 2007; Ohnishi et al., 2004; Son et al., 2011; Pei et al., 2016; Govindaraj & Sorimuthu, 2015.

(1g/day) did not exert demonstrable impacts on glycaemic control, inflammatory markers or oxidative stress among T2D patients after daily ingestion for 8 weeks (Azimi et al. 2014). In contrast, daily consumption of 2g dried and powdered rhizomes of turmeric (*Curcuma longa* L.) for 4 weeks resulted in reduced levels of fasting blood glucose and HbA1c, improved lipid profile and enhanced antioxidant status in T2D patients (Maithili Karpaga Selvi et al. 2015).

Conclusions

The clinical evidence included in this review sheds light on the potential benefits of using certain types of plant-based whole foods or their extracts as a nutritional or therapeutic measure in ameliorating diabetic conditions and preventing the disease advancement among T2D patients. In addition to the discussed mechanisms of actions of phytochemicals on diabetic conditions, an emerging notion related to phytochemicals' interactions on the Nuclear factor erythroid 2-related factor 2 (Nrf2) has added values to further understanding the mechanistic basis of phytochemicals' roles in dietary management of chronic diseases. Recent evidence has unveiled Nrf2's regulatory role in cellular resistance to oxidants. Acting as a transcription factor, it mediates the redox disturbances induced by environmental or endogenous factors through modulating the expression of multiple antioxidant response element (MRE)-dependent genes (Ma, 2013). Besides, Nrf2 is anti-inflammatory and its deficiency results in inflammation in an experimental setting (Johnson et al., 2010; Rangasamy et al., 2004, 2005; Garbin et al., 2009; Cho et al., 2004; He & Ma, 2012). This may be explained by the observed inhibitory actions of Nrf2 on the NF- κ B pathway and proinflammatory cytokine production (Li et al., 2008; Ma et al., 2003). However, further

research is still largely required to understand the exact anti-inflammatory mechanisms of Nrf2.

The phytochemicals that are considered to exert activity related to management of glycaemic control, or to prevention of diabetes-related complication, do so by acting on a variety of cellular targets and their effect often refers to transcription factors that are nodes in multiple signalling pathways. Polyphenolic flavonoids (notably EGGC) are prominently present in the literature on biologically active compounds with antidiabetic activity, as are berberine, and curcumin; in the context of drug discovery, all these compounds would be dismissed as pan assay interference substances (PAINS) (Baell & Walters, 2014; Baell 2016). Although individual reports may present models with clear looking signalling cascades, an overall review shows that PAINS alter numerous cell functions. Currently, there is little consensus and the mechanisms underlying antidiabetic activity are poorly understood. Arguably, many biologically active dietary products may act via rather non-specific mechanism like membrane bilayer perturbation (Ingólfsson et al., 2014). These properties make the listed biologically active dietary phytochemicals unattractive objects for drug discovery programs. However, they can still explain the mode of action of many dietary compounds in the prevention of diabetes-related complications or of degenerative diseases. Repeated low level activation of anti-inflammatory responses may be sufficient to maintain cellular homeostasis by avoiding peaks and troughs, e.g. by reducing post-prandial peaks in glucose levels and concomitant oxidative stress. In this view, ameliorating dietary compounds will never have the strength of therapeutic drugs like the sulfonylureas or metformin, and are not likely either to be lead-compounds for development of novel therapeutic drugs. However, dietary phytochemicals may exert a mild activity, enough to ‘nudge’ cells and tissues back to a physiologically healthy homeostasis, without causing harm in the long run.

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